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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/042,488	03/16/98	EVANS R	SALK1520-2

EXAMINER	
KAUSHAL,S	
ART UNIT	PAPER NUMBER
1633	11

DATE MAILED: 10/12/00

HM12/1012

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/042,488	Evans et al
Examiner	**Group Art Unit**
SUMESH KAUSHAL	1633

☒ Responsive to communication(s) filed on *Sep 3, 2000*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-46* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-46* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. The request filed on 09/13/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/042,488 is acceptable and a CPA has been established. An action on the CPA follows.

The applicant's response filed on Paper No. 10, 05/26/00 has been fully considered but they are not persuasive for the same reasons set forth in an earlier Official action mailed on 07/02/99.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use the invention** for the same reasons of record in Official action mailed 07/02/99.

Applicant's arguments filed 09/03/00 have been fully considered but they are not persuasive. The applicant argues that the PTO's reliance on Anderson WF (Nature 392:25-30, 1998) and Verma et al (Nature 389:239-242, 1997) related to Gene Therapy efficacy is without merit. The applicant further argues that recent reports providing details of several successful gene therapy treatment of human subjects supports the position that gene therapy methodology is effective technique to treat various disease conditions (response page 5). The applicant concluded that considering the references

cited one skilled in the art would have reasonable expectation of success to treat disease using gene therapy techniques (response page 6).

However, this is not found persuasive because the instant invention as claimed is drawn to a method of modulating the expression of an exogenous gene by creating ecdysone-inducible gene expression in a mammal subject. The invention as claimed requires the delivery of the ecdysone responsive receptor complex into a mammalian subject via viral and non viral methods, wherein the expression of a therapeutic gene is modulated by the administration of a formulation carrying an ecydsteroid and an activator for the silent partner of the receptor complex.

The claimed ecdysone inducible system comprises **RXR and EcR** which hetrodimerize and transactivate the ecdysone response element capable of driving the expression of a gene of interest (specification Fig-2). It is not clear how both RXR and EcR constructs are delivered into a single cell in a mammalian subject. The specification fails to provide any guidance to selectively target both constructs into a single cells in order to achieve ecdysteroid induced responsiveness. At the best the specification teaches ecdysone responsiveness in a cell line (293) **in vitro** via transient transfection of modified ecdysone receptor VpEcR, a hetrodimeric partner (RXR) and an ecdysone inducible reporter gene (example-3) which does not represent the modulation of the expression of an exogenous gene in a mammalian subject.

Furthermore, the applicant fails to provide any guidelines for determining which individual need to be administered with the formulation as claimed because an ecdysone inducible therapeutic gene should be in place in the host before the administration of any such formulation. Since, the presence of an ecdysone inducible system in a mammalian subject is the prerequisite of instant invention, it is not clear how one skilled in the art would use the invention as claimed without any reasonable expectation of success.

The applicants assertion that gene therapy is predicable art is not persuasive in view of official action mailed 07/02/99. The instant claims reads upon a method of modulating the expression of an exogenous gene in mammalian subject which requires the delivery of genes of interest into cells in vivo. The official action clearly states that gene therapy was regarded as highly unpredictable art because it has been difficult to predict the efficiency and out come of transduced therapeutic genes (Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997).

In addition, the art at the time of filing also teaches that ecdysone analogs varies in their hormonal potencies which results in the differential regulation of ecdysone induced gene expression. For example, 20-Hydrooxycdysone was found 100 time more active than ecdysone (Nakagawa et al Steroids 60(5):401-405, 1995; page 402. col.2, para.2 lin.1). The specification fails to provide guidance to dosage amount, dosage frequencies for any and all ecdysteroids, RXR agonist and antagonists formulations which results in the induction of any therapeutic gene in any mammalian subject.

Considering the unpredictability in the state of gene therapy art the specification as filed fails to disclose a single working example wherein expression of a wild type and/or therapeutic gene is modulated by transducing "an ecdysone inducible system" into a mammalian subject using a formulation comprising any and all types of ecdysteroids any activator for the silent partner of the receptor complex.

Thus, in view of lack of specific guidance in the specification and considering the state of undeveloped art, the skilled artisan at the time of filing would be unable to use the claimed invention, without an excessive and undue amount of experimentation. The experimentation required would

include the delivery of both RXR and EcR constructs into a single cell in a mammalian subject and subsequent modulation of the transduced ecdysone inducible system using the formulation comprising any and all naturally occurring ecdysones, ecdysone-analog and/or ecdysone mimics.

Claim Rejections - 35 USC § 102

Cancelled

Claims 25-29 and 31-34 remains rejected under 35 U.S.C. 102(b) as being anticipated by Meybeck et al (US Pat. No. 5198225, 3/30/93). Maybeck et al teaches a composition comprising at least one ecdysteriod or ecdysteroid derivatives in admixture with pharmaceutically acceptable excipient (see col.9, lin.57). Thus Meybeck et al clearly anticipate the claimed formulation. The applicant fails to address the above rejection in the response filed on Paper No. 10, 05/26/00.

Claim Rejections - 35 USC § 103

Cancelled

Claims 25-34 and 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meybeck et al (US Pat. No. 5198225, 3/30/93) and further in view of Mikitani (Biochem. Biophy. Res. Com. 227(2)427-432, 1996). Maybeck et al teaches a composition comprising at least one ecdysteriod or its derivatives in admixture with pharmaceutically acceptable excipient (see col.9, lin. 57). However, Maybeck et al does not teach the use of such composition comprising of a ecdysone mimic. Mikitani teaches the use of non steroidal ecdysone receptor ligand (3,5-di-tert-butyl-4-hydroxy-N-isobutyl-benzamide) binds to ecdysteroid receptor and regulates the expression of a ecdysone responsive gene. Mikitani also teaches the use of naturally occuring ecdysteroid 20-HE to regulate the expression of a marker gene in genetically enineered cells (page 429, fig-2b). Thus, Mayback teaching the formulation comprising an ecdysone hormone in pharmaceutically acceptable

excipient and Mikitani teaching the use of a ecdysone mimic, it would have been obvious to one with ordinary skilled in the art to make a formulation comprising ecdysone, ecdysone analogs or a ecdysone mimic. One would have been also motivated to use ecdysone mimics in a formulation because ecdysone mimic are readily available synthetic chemical compounds. The applicant fails to address the above rejection in the response filed on Paper No. 10, 05/26/00.

Conclusion

No claims are allowed.

1. All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned as (703) 308-2035. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

S. Kaushal, AU 1633